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10/553,373	03/22/2007	Paul Tardi	532552000102	3684	
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MORRISON & FOERSTER LLP		EXAMINER			
12531 HIGH BLUFF DRIVE		KISHORE, GOLLAMUDI S			
SUITE 100		ART UNIT	PAPER NUMBER		
SAN DIEGO, CA 92130-2040		1612			
NOTIFICATION DATE	DELIVERY MODE				
10/18/2011	ELECTRONIC				

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

EOfficeSD@mofo.com  
PatentDocket@mofo.com  
Dr Caldwell@mofo.com

<b>Office Action Summary</b>	<b>Application No.</b> 10/553,373	<b>Applicant(s)</b> TARDI ET AL.
	<b>Examiner</b> Gollamudi S. Kishore, PhD	<b>Art Unit</b> 1612

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) Responsive to communication(s) filed on 29 August 2011.
- 2a) This action is FINAL.      2b) This action is non-final.
- 3) An election was made by the applicant in response to a restriction requirement set forth during the interview on \_\_\_\_\_; the restriction requirement and election have been incorporated into this action.
- 4) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 5) Claim(s) 25-31,39-41,45-46 and 51-56 is/are pending in the application.
- 5a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 6) Claim(s) \_\_\_\_\_ is/are allowed.
- 7) Claim(s) 25-31,39-41,45-46 and 51-56 is/are rejected.
- 8) Claim(s) \_\_\_\_\_ is/are objected to.
- 9) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 10) The specification is objected to by the Examiner.
- 11) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 12) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 13) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All    b) Some \* c) None of:
  1. Certified copies of the priority documents have been received.
  2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO/SB/08)  
 Paper No(s)/Mail Date \_\_\_\_\_
- 4) Interview Summary (PTO-413)  
 Paper No(s)/Mail Date \_\_\_\_\_
- 5) Notice of Informal Patent Application
- 6) Other: \_\_\_\_\_

#### **DETAILED ACTION**

The amendment dated 8-29-11 is acknowledged.

Claims included in the prosecution are 25-31, 39-41, 45-46, 51-56.

The following are the rejections.

#### **Double Patenting**

1. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be

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commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

2. Claims 25-31, 39-40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 10-11, 13, 18-20, 41 and 45-46 of copending Application No. 10/417,631. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims in said copending application are drawn to liposomal compositions containing two anti-neoplastic agents in liposomes having at least 10 mole percent of either phosphatidylcholine, phosphatidylglycerol, phosphatidylserine or sphingomyelin or a combination of these whereas instant claims are generic with respect to the composition containing the anti-neoplastic agents. It would have been obvious to one of ordinary skill in the art to select the phospholipids and vary the amounts or use other carriers.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

3. Claims 41, 45-46 and 51-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of copending Application No. 11/701,326. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims in both applications are drawn to the same method of preparation of a composition which is

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non-antagonistic. Claims in the copending application are generic with respect to the assay conditions and therefore anticipate the cell culture assay or cell-free assay in instant claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

4. Claims 41, 45-46 and 51-56 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 14, 16-17, 22-23 and 26-28 of copending Application No. 11/304328. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims in both applications are drawn to the same method of preparation of a composition which is non-antagonistic. Claims in the copending application are generic with respect to the assay conditions and therefore, instant claims are anticipated by the claims in said copending application. Claims in said copending application are drawn to liposomes whereas instant claims are generic with respect to the composition containing the anti-neoplastic agents. It would have been obvious to one of ordinary skill in the art to use other carriers.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

5. Claims 25-31 and 39-40 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25-35 of copending Application No. 11/841,786. Although the conflicting claims are not identical, they are not patentably distinct from each other because claims in both applications are

drawn to the same compositions. Claims in the copending application are generic with respect to the assay conditions and therefore, instant claims are anticipated by the claims in said copending application. Claims in said copending application are drawn to liposomes whereas instant claims are generic with respect to the composition containing the anti-neoplastic agents. It would have been obvious to one of ordinary skill in the art to use other carriers.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

These double patenting rejections are maintained for the following reason:  
"Incorrect filing date; the correct date is 22 March 2007".

#### Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:  
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 51-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific combination of antineoplastic agents and specific liposomal compositions, does not reasonably provide enablement for claims as

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recited. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 8 USPQ2d, 1400 (Fed.Cir.1988). Among these factors are: (1) the nature of the invention; 2) the state of the prior art; 3) the relative skill of those in the art; 4) the predictability or unpredictability of the art; 5) the breadth of the claims; 6) the amount of direction or guidance presented; 7) the presence or absence of working examples; and 8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

- 1) The nature of the invention: the invention concerns with particulate compositions containing two neoplastic agents in mole ratios which are non-antagonistic when released into the host and methods of treatment of cancer.
- 2) The state of the prior art: the state of the prior art is very high in terms of formulating the liposomal or other particulate sustained release compositions and treating various disease states, but not releasing the two neoplastic agents in the same non-antagonistic ratios *in vivo* as determined *in vitro*.
- 3) The relative skill of those in the art: the skill of one of ordinary skill in the art is very high (Ph.D level technology).

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4) The predictability or unpredictability in the art: while there is general predictability in formulating the liposomal formulations containing single anti-neoplastic agent or a combination, there is unpredictability in the release of the two agents in a non-antagonistic ratio. This is because the anti-neoplastic agents can be either positively charged or negatively charged or neutral and the release rates in an antagonistic ratio will depend upon the nature of the agent and its interactions with the liposomal components. Furthermore, some of the agents are lipophilic and thus sequester in the lipid membrane while others are sequestered within the aqueous interior being hydrophilic. One would not expect the same release rates with two hydrophilic agents as opposed to one hydrophilic and one lipophilic active agent. Similar is the case with other particulate systems.

5). The breadth of the claims: instant claim is very broad in terms of the active agents and the cancers to be treated and the particulate systems which are supposed to release the agents in the same non-antagonistic ratios as determined in vitro. . Instant generic claims do not recite any specific active agents, specific components of particulate systems, specific liposomal components and the specific cancers to be treated.

6) The amount of direction of guidance provided: instant specification provides guidance just to prepare specific neoplastic agent combinations in specific liposomes and their effect in mice and nothing else.

- 7) The presence or absence of working examples: as pointed out above, instant specification provides guidance just to prepare specific neoplastic agent combinations in specific liposomes and their effect in mice and nothing else.
- 8) The quantity of experimentation necessary: it would require undue experimentation to determine which specific particulate or liposomal compositions are able to release a specific combination of two anti-neoplastic agents in the non-antagonistic ratios *in vivo* in the treatment of various cancers which the generic term encompasses in the same ratios as determined *in vitro*.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that the enclosed Declaration of Dr. Lawrence Mayer (Exhibit 1) attesting to the state of the art in regard to liposome design and that one of ordinary skill in the art would be able to design appropriate liposomes for the combination of an for any two drugs without undue experimentation. This argument is not persuasive since the declaration conveys only the personal opinion of Dr. Mayer which is not supported by any experimental data. Instant claims are drawn to numerous delivery vehicles such as liposome and/or lipid micelles and/or block copolymer micelles and/or polymer micro particles and/or polymer nanoparticles and/or polymer lipid hybrid systems and/or derivatized single chain polymers; these delivery vehicles are diverse and are structurally different. Liposomes are bilayer structures whereas micelles are single walled structures; polymer micro particles and nanoparticles are totally different from liposomes and micelles and furthermore, the release rate of active agents depends upon the nature of the polymer. It is unclear to the examiner as to how one can design

the delivery system which gives the same release rates of two active agents as that observed in vitro without undue experimentation. As already pointed out, in order to obtain the same release rates from liposomes based on the vitro release rates (which does not require liposomes), one has to design liposomes using specific phospholipids (even non-phospholipids in case of niosomes) when both agents are co-encapsulated within the same liposomes or different liposomes in which the active agents are separately encapsulated. The term, liposomes applies to unilamellar, multilamellar, paucilamellar, multivesicular liposomes and even niosomes. The examiner points out that Mayer's' own prior patent indicates that the release rates of doxorubicin depends upon the lipid composition and even the pH gradient (see col. 9, lines 28-61 and col. 12, lines 27-35 of US 6,083,530). It is interesting to note applicant's own statement on page 8 of the response that "the liposomes must be such that the administered non-antagonistic ratio is maintained in the blood for at least an hour. Not just any liposomal composition will do". Instant claims do not recite specific components of the liposomes and their ratios which are responsible of the release of the drugs in the desired ratios. If the release rates of one drug in the drug combination depends upon so many factors, one would expect these factors playing a role in the release of the second drug. One, thus, cannot determine the ratio of release rates which should be the same as in vitro ratios without undue experimentation. The examiner also points out that the term, anthracyclines' includes compounds with different functional groups and even morpholine anthracyclines (see 0008 of US 2003/0087839). Applicant has presented neither experimental evidence nor a clear rationale that irrespective of the nature the

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drugs in the drug combination, one can design liposomes which will maintain the same non-antagonistic ratios in vivo as observed in vitro.

"A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compositions fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471 ; In re Barr et al. (CCPA 1971 ) 444 F 2d 349, 151 USPQ 724."

It is still the examiner's position that what applicants have is a concept and designing the liposomes or other delivery vehicles which will maintain non-antagonistic ratios in vivo as observed in vitro rates without undue experimentation. The declarations provided by Joseph Bertino, Gerald Batist, John Lazo, William Hait and Alan Sartorelli have been fully considered, but are not found to be persuasive since they provide their personal opinions without any experimental evidence. The rejection is maintained.

#### Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) The invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 25-28, 30-31 are rejected under 35 U.S.C. 102(b) as being anticipated by Saxon (Journal of Liposome Research, 1999).

Instant claims are composition claims requiring two antineoplastic agents in delivery vehicles in mole ratios which exhibit a non-antagonistic cytotoxic effect. Saxon discloses the encapsulation of two anti-cancer drugs in liposomes. Since as pointed out above, a non-antagonistic effect (synergistic effect) depends on the cancer to be treated, the reference meets the requirements of instant claims. There are several types of cancers are known in the art and the burden is upon applicant to show that the combination suggested by Saxon is not in a non-antagonistic ratio against all the known types of cancers.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Saxon does not describe a composition comprising particulate delivery vehicles with first and second agents that maintain the administered ratio for at least one hour. According to applicant, as set forth on page 515, when vincristine and mitoxantrone were administered simultaneously in liposomes, within one hour, 90 % of vincristine was lost, but only 30 % of the mitoxantrone was lost and thus, the ratio was drastically altered in the plasma rather than maintained.

This argument is not found to be persuasive since instant claims do not recite exact ratios of the two neoplastic agents and applicant has not shown that what is released in Saxon (vincristine and mitoxantrone) is not in an non-antagonistic ratio.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. Claims 51-53 are rejected under 35 U.S.C. 103(a) as being unpatentable over Saxon cited above.

The teachings of Saxon have been discussed above. Instant claims are drawn to a method to treat a neoplastic disease or condition using the composition of claim 25 to human or mammals. Since the composition of Saxon is for the treatment of cancer, it would have been obvious to one of ordinary skill in the art to use the compositions of Saxon for the treatment of cancers with a reasonable expectation of success.

12. Claims 25-31, 39-41, 45-46 and 51-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Englom (British Journal of Cancer, 79 (2), 1999) or Kano (leukemia Research, vol. 17, 1993) or Guichard (Biochemical Pharmacology, vol. 55,

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1998), or WO 01/10416 in combination with applicant's statements of prior art record, in further combination Fountain (5,000,958).

Englom teaches additive and supra-additive cytotoxicity of cisplatin-taxane combination in ovarian carcinoma cell lines (Summary).

Kano teaches synergistic effects of carboplatin in combination with cytosine arabinoside, mitoxantrone and CPT-11 (Irinotecan) and additive effects of carboplatin in combination with bleomycin, daunorubicin, etoposide and others in human leukemia cell lines (abstract).

Guichard discloses synergistic activity of 5-fluoracil and Irinotecan in human colorectal carcinoma cell line (abstract).

WO teaches that chemotherapeutic agents such as carboplatin, cisplatin, paclitaxel, gemcitabine, and 5-fluorouracil can be used in combination (claim 12). In essence, these references teach the synergistic effect of drug combinations or combination of anti-neoplastic agents which could be used for treatment of cancer. What is lacking in these references are the use of various algorithms and analysis of the data using Chou-Talalay median-effect method and the use of liposomes as carriers.

Applicant on pages 20 and 21 state that various algorithm methods, Chou-Talalay median effect method to determine the synergistic activity of anti-cancer drugs is known in the art.

Fountain discloses co-encapsulation of two antimicrobial agents which are non-antagonistic in liposomes after evaluating their effect in combination in vitro (abstract, col. 7, line 45 through col. 8, line 5, Examples and claims).

Encapsulation of cisplatin-taxane combination taught by Englom, or carboplatin-several other anti-cancer drugs taught by Kano or Irinotecan drug combinations of Guichard or combination of anti-neoplastic agents taught by WO in mole ratios which are non-antagonistic after determining these ratios by art well known Chou-Talalay median effect method would have been obvious to one of ordinary skill in the art, with a reasonable expectation of success because Fountain teaches that one can encapsulate two drugs in liposomes after determining their non-antagonistic action in vitro.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that WO 01 is clearly inapposite as it merely states the acknowledged prior art that many treatments, especially for cancer, are combination treatments and that sustained release formulations can be used while the purpose of the invention is to improve such compositions by maintaining non-antagonistic ratios after administration. The examiner points out that WO is combined with other references to show that the claimed anti-neoplastic agents are known to be used in combination. With regard to maintaining the non-antagonistic ratios after administration, the examiner points out that Fountain clearly teaches such a concept.

Applicant argues that there is nothing in Fountain that describes the ratio as being maintained once administration is accomplished. This argument is not persuasive since Fountain is based on the same principle as instant application, that is, determining the in vitro non-antagonistic effect and based on that effect formulate liposomes with the same ratios. According to the tables II, III, VI and VII in Fountain, the administered liposomes this combination is very effective showing synergistic effect which implies

that the ratio of the released agents is similar to the in vitro ratios. Furthermore, instant claims recite, 'liposomes' and Fountain teaches liposomes. Applicant has not shown any experimental evidence showing that the liposomes of Fountain did not release the two active agents in the same way as in in vitro as in instant invention. It is interesting to note that applicant is claiming structurally dissimilar sustained release vehicles with the claims reciting a functional limitation without showing that all these sustained release vehicles will release the antineoplastic agents in vivo in the same ratios as in vitro.

13. Claims 25-31, 39-41, 45-46 and 51-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Englom (British Journal of Cancer, 79 (2), 1999) or Kano (leukemia Research, vol. 17, 1993) or Guichard (Biochemical Pharmacology, vol. 55, 1998) or WO 01/10416 in combination with applicant's statements of prior art record, in further combination with Vaage (Int. J. Cancer 1993), Saxon (Journal of Liposome Research) Bally (5,736,155) individually or in combination (all are of record), optionally in further combination with Fountain (5,000,958).

Englom teaches additive and supra-additive cytotoxicity of cisplatin-taxane combination in ovarian carcinoma cell lines (Summary).

Kano teaches synergistic effects of carboplatin in combination with cytosine arabinoside, mitoxantrone and CPT-11 (Irinotecan) and additive effects of carboplatin in combination with bleomycin, daunorubicin, etoposide and others in human leukemia cell lines (abstract).

Guichard discloses synergistic activity of 5-fluoracil and Irinotecan in human colorectal carcinoma cell line (abstract).

WO teaches that chemotherapeutic agents such as carboplatin, cisplatin, paclitaxel, gemcitabine, and 5-fluorouracil can be used in combination (claim 12). In essence, these references teach the synergistic effect of drug combinations. What is lacking in these references are the use of various algorithms and analysis of the data using Chou-Talalay median-effect method and the use of liposomes as carriers.

Applicant on pages 20 and 21 state that various algorithm methods, Chou-Talalay median effect method to determine the synergistic activity of anti-cancer drugs is known in the art.

Vaage et al teach compositions containing liposomes (vehicles) and encapsulated therein two therapeutic agents, vincristine and doxorubicin. The liposome sizes are 80 nm. According to Vaage, the liposome formulations are significantly more effective than the free drugs. (note the abstract, Materials and Methods and results). Vaage in addition teaches that a number of studies in animal models have shown that the therapeutic activities of anti-cancer drugs can be increased and prolonged and toxic effects reduced when they are encapsulated in liposomes (page 959, col. 1).

Saxon discloses compositions containing two cancer drugs encapsulated in liposomes. The drugs taught are vincristine and mitoxantrone. The diameter of the liposomes is between 100-120 nm. (Abstract and Materials and Methods).

Bally teaches that two antineoplastic agents can be co encapsulated within the liposomes (col. 15). The drugs taught include fluorouracil, cisplatin, doxorubicin, vincristine, vinblastine and others (col. 7).

Encapsulation of cisplatin-taxane combination taught by Englom, or carboplatin-several other anti-cancer drugs taught by Kano or Irinotecan drug combinations of Guichard or combination of anti-neoplastic agents taught by WO would have been obvious to one of ordinary skill in the art, with a reasonable expectation of success because the references of Saxon, and Bally each teach the knowledge in the art of encapsulation of both agents in liposomes or because of the advantages of liposomes such as reduced toxicity taught by Vaage. The use of art known algorithms and analysis of the data such as Chou-Talalay median-effect method to determine the non-antagonist ratio with a reasonable expectation of success would have been obvious to one of ordinary skill in the art since they are known to be practiced in the art. One of ordinary skill in the art would be further motivated to determine the mole ratios which are non-antagonistic in vitro by art well known Chou-Talalay median effect method and encapsulate these agents in those ratios with a reasonable expectation of success because Fountain teaches that one can encapsulate two drugs in liposomes after determining their non-antagonistic action in vitro.

Applicant's arguments have been fully considered, but are not found to be persuasive. The examiner has already addressed applicant's arguments regarding the primary references. Applicant argues that Vaage also teaches away from the central concept of the invention; this argument is not persuasive since Vaage is combined for its teachings of co-encapsulation of two anti-neoplastic agents and one of ordinary skill in the art would be motivated to determine the in vitro effective ratios and then formulate them in liposomes as advocated by Fountain. Applicant's arguments with regard to Bally

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are not persuasive since this reference is combined for its teachings of the combination of various anti-neoplastic agents and not for its release rates.

14. Claims 25-31, 39-41, 45-46 and 51-56 are rejected under 35 U.S.C. 103(a) as being unpatentable over Englom (British Journal of Cancer, 79 (2), 1999) or Kano (leukemia Research, vol. 17, 1993) or Guichard (Biochemical Pharmacology, vol. 55, 1998) or WO 01/10416 in combination with applicant's statements of prior art record, in further combination with Vaage, Saxon (Journal of Liposome Research) Bally (5,736,155) individually or in combination as set forth above, further in view of Giles (US2003/0083316) of record, optionally further in view of Fountain (5,000,958).

The teachings of Englom, Kano, Guichard, WO, applicant's statements of prior art, Vaage, Saxon have been discussed above.

Giles while disclosing a pharmaceutical combination for the treatment of cancer using OddC and Ara-C teaches first determination of the effect of the combination in CRRF\_CEM cells. To determine if the combination is additive, antagonistic or synergistic, a linear cure fitting was used, using the CalcuSyn software which is based on algorithms developed by Chou and Talalay (Examples, Example 3 in particular). The use of art known algorithms and analysis of the data such as Chou-Talalay median-effect method to determine the non-antagonist ratio with a reasonable expectation of success would have been obvious to one of ordinary skill in the art since the reference of Giles shows that this method is used to determine the effect is additive, antagonistic or synergistic. One of ordinary skill in the art would be further motivated to determine the mole ratios which are non-antagonistic in vitro by art well known Chou-Talalay

median effect method and encapsulate these agents in those ratios with a reasonable expectation of success because Fountain teaches that one can encapsulate two drugs in liposomes after determining their non-antagonistic action in vitro.

Applicant provides no specific arguments for this rejection.

**15. THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to GOLLAMUDI S. KISHORE whose telephone number is (571)272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore/

Primary Examiner, Art Unit 1612

GSK

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 29-32 and 35-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vaage (Int. J. Cancer 1993) in combination with Campbell (US 2002/0090392), optionally in combination with WO 01/10416 and/Bally (5,736,155). Instant claims are composition claims with functional limitations of their non-antagonistic release ratio profiles and said compositions containing liposomally encapsulated anthracycline and a second antineoplastic agent which is either FU, FUDR or AraC (cytarabine).

Vaage et al teach compositions containing liposomes (vehicles) and encapsulated therein two therapeutic agents, vincristine and doxorubicin. The liposome sizes are 80 nm. According to Vaage, the liposome formulations are significantly more effective than the free drugs. (Note the abstract, Materials and Methods and results). Vaage in

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addition teaches that a number of studies in animal models have shown that the therapeutic activities of anti-cancer drugs can be increased and prolonged and toxic effects reduced when they are encapsulated in liposomes (page 959, col. 1).

Vaage however, does not teach doxorubicin in combination with AraC (Cytarabine) or fluorouracil.

Campbell while disclosing drug delivery formulations teaches that liposomes can be used to encapsulate chemotherapeutic drugs such as doxorubicin, vincristine, 5 fluorouracil and cytarabine (Abstract, 0023, 0030-0033).

WO teaches that chemotherapeutic agents such as doxorubicin and 5-fluorouracil can be used in combination (claim 12).

Bally teaches that two antineoplastic agents can be co encapsulated within the liposomes (col. 15). The drugs taught include fluorouracil, cisplatin, doxorubicin, vincristine, vinblastine and others (col. 7).

To prepare a liposomal composition containing encapsulated doxorubicin as well as encapsulated 5 fluorouracil or cytarabine would have been obvious to ordinary skill in the art since Campbell teaches the equivalency between vincristine and either fluorouracil or cytarabine.

To prepare liposomal compositions containing doxorubicin and either 5-FU or AraC instead of vincristine taught by Vaage would have been obvious to one of ordinary skill in the art since Campbell and Bally each teach the equivalency between vincristine and fluorouracil. One of ordinary skill in the art would be motivated to a combination therapy since both WO and Bally both teach the use of combination therapy, Bally in particular

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teaches the combination therapy using liposomally co-encapsulated doxorubicin and 5 FU.

Applicant amends the claims to delete 'synergistic' to introduce 'non-antagonistic' and define this term to include both synergistic as well as additive effects. Therefore, even assuming that the in vitro release ratios of these two active agents is not the same as in vitro release rates, since Vaage, Bally and Campbell teach liposomal formulations, the burden is upon applicants to show that the effect of the drugs is not at least additive. Furthermore, as pointed out above, a non-antagonistic effect (synergistic effect or additive effect) depends on the cancer to be treated. There are several types of cancers are known in the art and the burden is upon applicant to show that the combination suggested by Saxon is not in a non-antagonistic ratio against at least some of the known types of cancers.

8. Claims 29-32 and 35-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Vaage (Int. J. Cancer 1993) in combination with Campbell (US 2002/0090392), optionally in combination with WO 01/10416 and/Bally (5,736,155) as set forth above, in further combination with applicant's statements of prior art and Giles (US2003/0083316) optionally further in view of Fountain (5,000,958).

The teachings of Vaage, Campbell, WO and Bally have been discussed above. What is lacking in these references is the teaching of in vitro testing method.

Applicant on pages 20 and 21 state that various algorithm methods, Chou-Talalay median effect method to determine the synergistic activity of anti-cancer drugs is known in the art.

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Giles while disclosing a pharmaceutical combination for the treatment of cancer using OddC and Ara-C teaches first determination of the effect of the combination in CRRF\_CEM cells. To determine if the combination is additive, antagonistic or synergistic, a linear cure fitting was used, using the CalcuSyn software which is based on algorithms developed by Chou and Talalay (Examples, Example 3 in particular). Fountain discloses the concept of co-encapsulation of two antimicrobial agents which are non-antagonistic in liposomes after evaluating their effect in combination in vitro (abstract, col. 7, line 45 through col. 8, line 5, Examples and claims).

The use of art known algorithms and analysis of the data such as Chou-Talalay median-effect method to determine the non-antagonist ratio with a reasonable expectation of success would have been obvious to one of ordinary skill in the art since the reference of Giles shows that this method is used to determine the effect is additive, antagonistic or synergistic. One of ordinary skill in the art would be further motivated to determine the mole ratios which are non-antagonistic in vitro by art well known Chou-Talalay median effect method and encapsulate these agents in those ratios with a reasonable expectation of success because Fountain teaches that one can encapsulate two drugs in liposomes after determining their non-antagonistic action in vitro.

9. Claims 29-32 and 35-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bally (5,736,155) in further combination with applicant's statements of prior art and Giles (US2003/0083316) optionally further in view of Fountain (5,000,958).

Bally teaches three different liposomal formulations encapsulating Adriamycin (doxorubicin) (Table II on col. II) and a combination of Adriamycin with cytosine arabinocye (Table I). Bally further teaches that two antineoplastic agents can be co encapsulated within the liposomes (col. 15). The drugs taught include fluorouracil, cisplatin, doxorubicin, daunorubicin, vincristine, vinblastine and others (col. 7).

Applicant on pages 20 and 21 state that various algorithm methods, Chou-Talalay median effect method to determine the synergistic activity of anti-cancer drugs is known in the art.

Giles while disclosing a pharmaceutical combination for the treatment of cancer using OddC and Ara-C teaches first determination of the effect of the combination in CRRF\_CEM cells. To determine if the combination is additive, antagonistic or synergistic, a linear cure fitting was used, using the CalcuSyn software which is based on algorithms developed by Chou and Talalay (Examples, Example 3 in particular).

Fountain discloses the concept of co-encapsulation of two antimicrobial agents which are non-antagonistic in liposomes after evaluating their effect in combination in vitro (abstract, col. 7, line 45 through col. 8, line 5, Examples and claims).

The use of art known algorithms and analysis of the data such as Chou-Talalay median-effect method to determine the non-antagonist ratio of the drugs in 3 different formulations taught by Bally with a reasonable expectation of success would have been obvious to one of ordinary skill in the art since the reference of Giles shows that this method is used to determine the effect is additive, antagonistic or synergistic. One of ordinary skill in the art would be further motivated to determine the mole ratios which

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are non-antagonistic in vitro by art well known Chou-Talalay median effect method and encapsulate these agents in those ratios with a reasonable expectation of success because Fountain teaches that one can encapsulate two drugs in liposomes after determining their non-antagonistic action in vitro. Furthermore, as pointed out above, a non-antagonistic effect (synergistic effect or additive effect) depends on the cancer to be treated. There are several types of cancers are known in the art and the burden is upon applicant to show that the combination suggested by Saxon is not in a non-antagonistic ratio against at least some of the known types of cancers.